International Journal of Pharmaceutical Chemistry
ISSN: 2249-734X (Online)
CODEN: IJPCH3 (American Chemical Society)
Journal DOI: https://doi.org/10.7439/ijpc
Research Article

Synthesis of New Barbiturate Esters derivatives as Intravenous Anesthetics: A new Dimension of Anesthesia Route: Part-II*

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***Article History:**
Received: 25/03/2018
Revised: 03/04/2018
Accepted: 03/04/2018
DOI: https://doi.org/10.7439/ijpc.v8i3.4761

Abstract

Conventional 1-methyl-2-oxobarbiturates and 1-methyl-2-thiobarbituates which are employed as anesthetics tend to accumulate in the body due to their slow rate of metabolism. As a result, the use of these compounds is restricted to either as an induction agent for anesthesia, subsequently maintained by volatile anesthetics or to short surgical procedures only. In order to overcome the limitations of application of barbiturates as general anesthetics, avoiding the use of volatile agents, an attempt was made to the structural modifications of barbiturates molecules as intravenous anesthetics. In view of these contexts, it was conceived that, by incorporating metabolically labile ester functions in one or both of the side chain of barbiturates ring system, it could be achieved. Since this procedure could diminish the likelihood of barbiturates to be accumulated in the body, it might be possible to get safer barbiturate intravenous anesthetics. This classification arose from the observation that whilst the biological properties of some drugs are extremely sensitive to minor changes in stereo-chemical feature, electron distribution and substituent, there are many other drugs which exhibit similar patterns of biological behavior, despite a wide diversity in their chemical configurations. This has been appeared to be the case with the barbiturate esters as discussed in this communication.

Keywords: Barbiturates, Intravenous anesthetics, Metabolically labile ester.

1. Introduction

The currently acceptable explanation of the short action of barbiturate anesthetics is that the distribution of drugs within the body components and to some degree of metabolism. It is, however, known that barbiturate anesthetics are not rapidly metabolized in the body. It was assumed that it could be possible to provide barbiturate anesthetics through molecular modifications which would undergo rapid metabolism and thereby offer very important clinical advantage. It was thought that there was a need for an agent that is potent, very brief because of rapid metabolic breakdown and allows restoration of all mental faculties within few hours, without persistent hangover or headache.

The first barbiturate used as intravenous anesthetics was hexobarbitone, but this was quickly replaced by shorter acting thiopentone. But due to its very short duration of action, its use remained limited to simple surgical procedure lasting for few minutes. Besides, thiopentone tend to accumulate in the body, its use was limited to that of induction agent only and in addition considerable cautions had to be taken by the anesthesists in view of its lower therapeutic index.

It was presumed that the activity of barbiturates could be modified by altering their lipid solubility. This may be achieved either by introducing suitable alkyl or aryl groups in side chain or alkylation or arylation of ring nitrogen and also by substitution of one of the ring oxygen by sulfur or selenium. Mautner [1] reported that by increasing the side chain length up to eight carbon atoms, both potency and lipophilicity rise and beyond eight carbon atoms, produces convulsion and in many cases result inactive compounds. A probable explanation is that the

lipid solubility has reached at such a level that the drugs are unable to reach at its targets. It is known that the presence of ester function in many drugs such as cholinergic, anti-cholinergic and local anesthetics are responsible for the susceptibility of these drugs to the action of plasma esterase and as such these compounds are rapidly metabolized. Further the introduction of ester functions in the decamethylene chain of the neuromuscular blocking agent decamethonium has been exploited to overcome the prolonged action of this compound. The resulting drug suxamethonium is widely used in surgery.

The currently accepted explanation of the short action of barbiturate anesthetic could be due to distribution of the drug in fat within the body component and a small fraction is metabolized. But it is known that barbiturates are not so easily metabolized. As it is known that the presence of ester function is susceptible for rapid metabolism, it was assumed that by modification of barbiturates by introducing ester functions in their side chain could provide such drugs which undergo rapid metabolism and thereby would offer very important clinical advantage. In view of this context six barbiturate esters were synthesized and their results reported [2]. This communication lists 31 barbiturate esters (Table-II) and table-(1V) of 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid (alcohol) and (carboxylic acid) in order of decreasing potency. The selection of esters took into account of pie substituent constants of C. Hansch [3] and preclinical screened results of compounds were available from the laboratory. As a result the preparation of unnecessary molecules was avoided.

2. Experimental

2.1 Melting point measurement: Melting points were recorded by Reichert's microscopic melting point apparatus.

2.2 Thin Layer Chromatography: Extemporaneously prepared silica gel plates by MN-
Duren, Kieselgel G-HR and readymade plates MN-Duren Polygram sil G/UV 254 both were found satisfactory.

2.3 Development reagent: 1:1 Ratio of chloroform and acetone

Spray reagent: Saturated aqueous solution of silver acetate and Diphenylcarbazone in 10% aqueous ethanol.

2.4 Experimental animals:

Male mice (CFLP), weight between 18-20g and Dutch Albino rabbits weight, between 1-2 kg. Drugs were administered intravenously as sodium salts in physiological saline to experimental animals. Elemental analyses were done in the Department of Chemistry, Strathclyde University, Glasgow UK. Biological studies were done by Mr. Neil Duff at Aspro- Nicholas Laboratories, Slough, England.

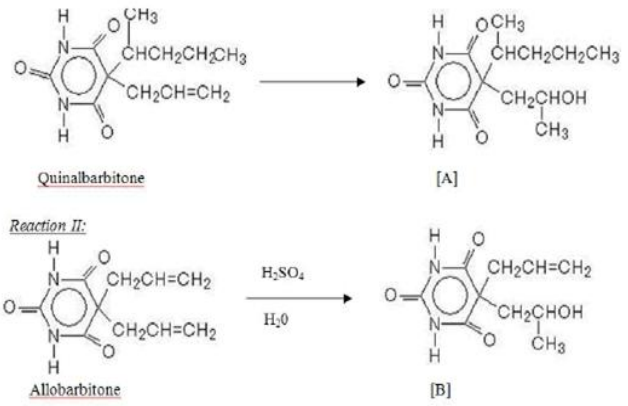
2.5 Compound number: refers to experimental protocol numbers.

2.6 Synthetic procedure

Literature search revealed that 5-alkyl-5-allyl barbiturate could be converted to 5-alkyl-5-(2-hydroxypropyl)-barbiturate. Thus, [5-{(2R)-pentan-2-yl(5-prop-2enyl-1,3-diazinane-2,4,6-trione)}] (quinalbarbitone) and [5-5-diprop-2-enyl-1,3-diazinane-2,4,6-trione] (allobarbitone) were converted into 5-{(1-methylbutyl)-(2-hydroxypropyl)} barbituric acid (A) and 5-{allyl-5-(2-hydroxypropyl)} barbituric acid(B) respectively. These hydroxyl barbiturates were transformed to esters by introducing different alkyl and aryl groups, their structures were confirmed by chemical analysis and biological screening was carried out.

2.7 Synthesis of 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid alcohol (A):

25g of quinalbarbitone was taken in RB flask; 25 ml conc. Sulfuric acid was added into it at RT (25^0C) and stirred continuously for 30 minutes. The deep red colored solution was put into a conical flask containing 200ml iced water. On keeping for about 30-45 minutes, crystalline solid appeared which was filtered, washed with iced cooled water, dried in air for 2-3 hours and finally dried at 60-70^0C for 2 hours and purified to get compound (A).



2.8 Purification of compound (A):

The solid product thus obtained was dissolved in boiled water and activated charcoal (5-7%) was added to the hot solution, stirred for 10 minutes and filtered off the charcoal. On cooling the filtrate at RT fine crystals of compound (A) were appeared, washed with hot water and dried in the oven at 80-85^0C to get moisture free white crystalline compound (20g; 74.5%), mp. 191-93^0C(lit.204^{o}C).

Analysed: Found C, 56.60; H, 7.90; N, 10.85 and O, 24.65. $C_{12}H_{20}N_2O_4$ **requires:** C, 56.00; H, 7.90, N, 10.90 and O, 25.2%. R_f value 0.50

2.9 Synthesis of 5-allyl-5-(2-hydroxypropyl) barbituric acid (B):

Allobarbitone (10g) was treated with conc. Sulfuric acid (20ml) for 5 minutes at 25^0C. The acidic solution was poured into iced water (100ml) and kept it for 8 hours when crystalline solid appeared. The product was filtered, washed with distilled water, dried in air, re-crystallized from diethyl ether and dried as in (A) to get moisture free colorless compound (B).

Analysed: Found: C, 53.00; H, 5.90; N, 12.10 and O, 29.00%. $C_{10}H_{14}N_4O_4$ **requires:** C, 53.00, H, 6.20, N, 12.4, and O, 28.4%. R_f. value 0.43

2.10 Synthesis of Esters from compound (A):

The resulting hydroxyl compounds (A) were esterified by conventional methods and six barbiturate esters proved to be short acting anesthetics with marked improvement in both potency and duration of action [4].

The choice of esters and its 5-alkyl substituent took into account of Hansch [3] pie constants relating to the potency of hypnotic barbiturates to their octanol-water partition co-efficient.

2.11 Synthesis of second series of compounds from (A):

Compound (52): 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid phenylacetate:

Phenyl acetic acid (2g) was mixed with the barbiturate alcohol (42A, 2g) at 80^0C until it was dissolved. The solution was then treated with 2-3 drops of concentrated sulfuric acid and refluxed for 6-7 hours. The refluxed solution was cooled at room temp (25^0C), diluted with iced-cold water (25ml), extracted with diethyl ether (25ml). The ethereal solution was washed with sodium hydrogen carbonate solution in water (25ml), dried over anhydrous sodium sulfate (Na_2SO_4) and solvent was removed. The semisolid mass thus obtained was put to column chromatography using basic Alumina. The 2% ethanol in ether eluate after drying and crystallization from ether-petroleum (40-60^0C) gave needles of 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid phenylacetate (2.15g; 73.5%), mp 137-38^0C. Found: C, 64.00; H, 7.00 and N, 7.40%. $C_{20}H_{26}N_2O_5$ requires C, 62.20; H, 7.00 and N, 7.50%. Rf.0.54

Compound (53): 5-(1-mthylbutyl)-5-(2-hydroxypropyl) barbituric acid valerate:

The barbiturate alcohol (40) 2.0g and valeric acid (10ml) containing 2-3 drops conc. Sulfuric acid and refluxed for six hours. The valerate ester (2.0g, 75%) was obtained as oil; Rf.0.60

Compound (58): 5-(1-methyl butyl)-5-(2-hydroxypropyl) barbituric acid cyclohexanate : The barbiturate alcohol (40) 2.0g, cyclohexane carboxylic acid 1.0g and a few drops of conc. Sulfuric acid were refluxed with stirring for six hours. The 2% ethanol in ether eluate from basic alumina column and on crystallization gave 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid cycloheanate (1.20g; 40%), mp. 168-70^0C. Found: C, 62.35; H, 8.25 and N, 7.65%. Rf.0.65

Compound (59): 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid 4'-methylvalerate. The barbiturate alcohol (**A**) 2.0g and 4'-methylvaleric acid (1.0g) and a few drops of conc. Sulfuric were refluxed for 6hrs; solvent was removed from the reaction mixture and chromatograhed over basic alumina. The 2% ethanol ether eluate on crystallization from ether-petrolium ether (40-60^0C) afforded ester (59) as fine needles, mp 130-32^0C (1.3g; 47%). Found: C, 60.90; H, 8.60 and $C_{18}H_{30}N_2O_5$ requires C, 61.0 and H, 8.5%.

Compound (67): 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid isobutyrate: The barbiturate alcohol (40) 2.0g, isobutyric acid 2.0g and a few drops of concentrated sulfuric acid were refluxed for 6h. The 2% ethanol in ether eluate from basic alumina column afforded an oil mass which on crystallisation from ether-petroleum ether (40-60^0C) gave colorless crystals of 5-(1-methylbutyl)-5-(hydroxypropyl) barbituric acid iso-butyrate (1.3g; 51%), mp. 140-42^0 C. Found: C, 56.90, H, 8.00 and N, 8.60%; Rf.0.54.

2.12 Synthesis of 5-ethyl-5-allyl barbituric acid:

Diethyl allylethyl malonate (100g) was run into a solution of metallic sodium (10g) in absolute alcohol (50ml) to which a saturated ethanol solution of urea (26.2g) was added. The reaction mixture was refluxed for 6h and the solvent was distilled off under vacuum. The solid mass was dissolved in water, extracted with diethyl ether to remove any un-reacted malonate before acidifying with dilute hydrochloric acid (20%). The solid crystals thus obtained were washed with water, dried in an oven at 100^0 C and on re-crystallization from dilute ethanol gave needles of 5-ethyl-5-allyl barbituric acid (61.0 g;71%) , 153-55^0 C. Found: C,55.10; H, 6.10 and N, 14.20%. $C_9H_{12}N_2O_3$ requires; C55.10, H, 6.10 and N, 14.3%.

Compound (70): 5-ethyl-5- (2-hydroxypropyl) barbituric acid phenyl acetate. A few drops of Conc. Sulfuric acid was added to the solution of barbiturate alcohol (2g) and phenyl acetic acid (1.28g) and the reaction mixture were refluxed for 6h. The solid was triturated with water, the ethereal layer washed with water and dried over anhydrous Na_2SO_4. The ethereal solution was chromatographed over basic alumina, 2% ethanol in ether eluate was evaporated and re-crystallised from ether-pet ether (40-60^0C) to provide compound **70**, (1.86g), mp 132-33^0C. Found: C, 61.30; H, 6.00; N, 8.45%. $C_{17}H_{20}N_2O_5$ requires: C, 61.40; H, 6.00 and N, 8.40%, Rf.0.52

Compound (71): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid butyrate.

The barbiturate alcohol (2g) was refluxed in butyric anhydride (4ml) as in compound **70.** The ether fraction of column chromatography in alumina was crystallized from ether-pet-ether (40-60^{0}C) gave compound **71**(1.87g; 70.5%) as needles, mp 143-44^{0}C. Found: C, 55.30; H, 7.00 and N, 9.70%. $C_{13}H_{20}N_2O_5$ requires: C, 54.90; H, 7.00 and N, 9.85%.

Compound (72): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid isobutyrate:

The barbiturate alcohol (0.82g) and isobutyric acid were refluxed for 6h as in **70**. The ether fraction from column chromatography was dried and crystallized from ether: pet-ether (40-60^{0}C) to give needles of compound **72**, (1.83g; 69%), mp 132-133. Found: C, 54.55; H, 7.00 and N, 10.10%. $C_{13}H_{22}N_2O_5$ requires: C, 54.90, H, 7.00; N, 9.85%.

Compound (73): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid pivalate:

To the barbiturate alcohol (2g) in pyridine (1.60g) was added pivaloyl chloride (2.10g) and the mixture was refluxed for 6h. Water was added to the resultant reaction, extracted with ether. The ethereal solution was washed with water, dried by adding anhydrous Na_2SO_4, filtered and solvent removed to get brown oily mass. This oily mass was chromatographed over basic alumina and the 2% ethanol in ether fraction upon crystallization from ether pet-ether (40-60%) produced colorless compound **73**, (1.63; 57%), mp 178-80^{0}C. Found: C, 56.00; H, 7.2; N, 9.80%. $C_{14}H_{23}N_2O_5$ requires: C, 56.40; H, 7.40 and N, 9.70%.

Compound (74): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid propionate:

The barbiturate alcohol (2g) was refluxed in propionic anhydride (6ml) for6h. The oily product obtained after removal of solvent was chromatographed over basic alumina and the ether eluate on crystallization from ether: pet-ether (40-60^{0}C), yielded needles of compound **74** (1.40g; 56%), mp.129-130^{0}C. Found: C, 53.45; H, 6.70 and N, 10.30%. $C_{12}H_{18}N_2O_5$ requires: C, 53.30; H, 6.63 and N, 10.30%.

Compound (75): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid valerate:

The barbiturate alcohol (2g), valeric acid (4g) and conc. Sulfuric acid (3-4 drops) were refluxed for 6h. To the reaction mixture iced-cooled water was added and extracted with- ether. The ether was distilled off, the oily mass was chromatographed over basic alumina and the 2% ethanol in ether fraction after crystallistion from ether-pet-ether (40-60^0 C) afforded fine needles of compound **74** (1.40g; 50%) mp. 143-45^{0}C. Found: C, 53.35; H, 7.40; N, 9.70%. $C_{14}H_{22}N_2O_5$ requires: C, 35.40; H, 7.40; N, 9.70%.

Compound (76): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid iso-valerate: The experimental procedure was similar as in compound **75** and the reaction afforded fine needles of compound **76** (1.41g; 50%); mp. 129-31^{0}C. Found: C, 56.65; H, 7.60 and N, 9.40%. $C_{14}H_{22}N_2O_5$ requires: C, 56.40; H, 7.40 and N, 9.70%.

Compound (77): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid vinyl acetate:

The barbiturate alcohol(2g) and vinyl acetic acid(2g) were refluxed in presence of a few drops of conc. Sulfuric acid and worked out as in compound **76** when colourless crystals of compound **77** produced (1.41g; 53%), mp. 125-26^{0}C. Found: C, 55.00; H, 6.00 and N, 9.90%. $C_{13}H_{18}N_2O_5$ requires: C, 55.30; H, 6.40 and N, 9.90%.

Compound (78): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid decanoate:

The barbiturate alcohol(2g) and decanoic acid(2g) were refluxed in the presence a few drops of conc. Sulfuric acid and worked out as in compound **76** when long needles of compound **78** was obtained (1.41g; 41%) 106-108^{0}C. Found: C, 62.40; H, 8.75 and N, 7.70%. $C_{19}H_{32}N_2O_5$ requires: C, 62.00; H, 8.70 and N, 7.60%.

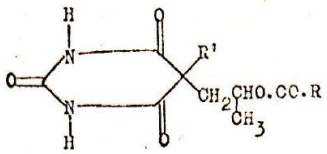
Compound (79): 5-Ethyl-5-(2-hydroxypropyl) barbituric acid laurate: The procedure applied is similar to compound **76,** using lauric acid.

3. Results and Discussion

The first batches of esters in table-II to be evaluated were compounds **52-57.** Compound **53**, the butyl ester was selected in order to see the effects of chain lengths of the series of compounds **46-48**, where maximum potency occurred with the propyl ester **47** (Table-I)[4]. The diminution of potency of compound **53** suggested that the optimal chain length had been exceeded. Compounds **54** and **57** were prepared to find the effects of chain branching. Despite of having similar pie value of their substituent chain lengths and increase in potency was observed. The question inevitably arose as to whether chain branching influenced potency due to steric or electronic factors. Reference to table-II shows that although both compounds **54** and 57 have high negative Es values, indicative of their bulkiness, the highly potent compound **52**, having similar pie value to compound **54** do not have high negative Es value. The question now arose how potent the compound **57** was as it has very brief duration of action at a dose level of 100mg/kg. This could be explained as that rapid metabolic breakdown prevented adequate blood level being maintained, as such the intrinsic activity of the compound could not been seen to its full extent. To get proper explanation for this question of separating structural factors influencing potency and duration of action, extended works need to be carried out. The selection of compounds **52** and **55** was based on the need to know the effect of benzyl and phenyl functions in view of their varying susceptibility towards chemical hydrolysis. It was found that potency of

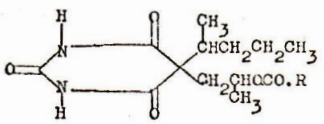
benzyl ester **52** was increased reasonably than that of phenyl ester **55** but both esters showed similar duration of action. However, the phenyl ester **55** failed induce anesthesia at the dose level in the screening procedure. The lack of potency of phenyl ester could be explained as due its rapid breakdown as many other esters appeared to be inactive. Compounds **56-69** were prepared to investigate a diverse range of esters covering a variety of structural types in hope of finding more potent short acting compounds of the series. The results in (table-II) reflected that little benefit was gained from this exercise, Table-II. The relationship between estimated duration of action at twice the anesthetic dose and electronic (sigma*) as well as steric (Es) parameters were observed in another series of compounds (Table-III) in those instances where values of both parameters were known. Since the duration of action of a drug at the 100% anesthetic dose may sometimes be relatively short as this dose being the minimal one ensuring anesthesia in all test animals, the comparison at twice the 100% anesthesia dosage was assumed to be more reliable indicator as far as duration of action is concerned Table-III. Once again the benzyl esters Compound **70** (table-1V), was the most potent member of the series. Since the log P value of this compound was dissimilar from that of the corresponding benzyl ester in the 1-methylbutyl series (table-1V), it was evident that the potency of these two esters could not relative to their log P values. This could be explained that the compound **70** was not screened at lower dose level. The compounds in (table -1V) were selected with a view to draw comparison with those tested in (table-II). Compounds **78** and **79** were included to assess further higher log P values in this series. To substantiate this contention is that overall lack of potency of the 5-ethyl series was attributed to the diminished pie values of ethyl side chain compared to the 1-methylbutyl group Table-1V.

Table I: Effects of chain lengths of the series of compounds



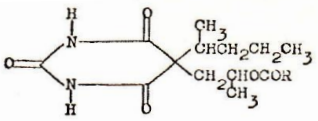
Compound No.	R'	R	Dose mg/kg	% Anaesth.	Duration in mins.	% death
46	$-CH(CH_3)CH_2CH_2CH_3$	$-CH_3$	300	-	-	
47	"	$-C_2H_5$	100	-	-	
			200	50	4.0	
			300	100	13.65	
48	"	$-(CH_2)_2CH_3$	100	70	3.17	
			166.7	100	6.67	
			300	100	13.75	40
49	$-CH_2CH=CH_2$	$-CH_3$	300	-	-	
50	"	$-C_2H_5$	300	-	-	
51	"	$-(CH_2)_2CH_3$	300	-	-	
Thiopentone			30	-	-	
			40	100	3.0	
			60	100	46.56±7.4	10
			70	100	37 ± 6.9	
			80	100	-	90
			100	-	-	100
Pentobarbitone			30	50	15.35	
			40	100	26.25	
			50	100	30.10	
			60	100	53	10
			80	100	112	30
			100	100	-	90

Table II: List of 31 barbiturate esters



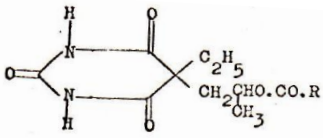
Compound No.	R	π	E_s	σ^*	Dose mg/kg	% Anaesth.	Duration in mins.	% death
52	$-CH_2C_6H_5$	2.27	-0.38	0.22	50	70	5.4 ± 1.93	
					60	100	16.5 ± 2.86	
					75	100	31.3 ± 4.16	
					100	100	69.15 ± 5.59	
					120	100	90.8 ± 8.47	
					150	100	79.2 ± 8.69	
57	$-C(CH_3)_3$	1.98	-1.54	-0.30	100	100	3.0	
					150	100	15.8 ± 2.82	
					200	100	30.10 ± 2.12	
54	$-CH(C_2H_5)_2$	2.30	-1.98	-0.23	100	100	13.6	
					150	100	19.69 ± 2.20	
					200	100	32.62 ± 3.03	
61	$-CH(C_6H_5)C_2H_5$	3.07	-1.50	0.04	50	-	-	
					100	100	16.3	
					200	100	96.0	
62[m]	$-CH(C_6H_5)_2$	3.84	-1.76	0.41	50	-	-	
					100	100	12.6	
					200	100	100.0	
58[m]	cyclo-C_6H_{11}	2.51	-0.79	-0.15	50	-	-	
					100	100	6.0	
					200	100	18.0	30(100)
59[m]	$-(CH_2)_2CH(CH_3)_2$	2.30	-0.34		100	100	8.0	20(100)
64	$-CH=CH-C_6H_5$	2.57		0.41	50	-	-	
					100	100	39.3	
					50	-	-	
60	$-CH_2C_6H_4OCH_3$	1.80			100	80	10.0	10
48	$-(CH_2)_2CH_3$	1.50	-0.36	-0.12	100	70	3.17	
					166.7	100	6.67	
					300	100	13.75	40
67	$-CH(CH_3)_2$	1.30	-0.47	-0.19	100	-	-	
					150	100	4.5	
					200	100	15.9	(10)
					300	100	19.6	10
69	$-OC_2H_5$				50	-	-	
					100	50	5.0	10
63[m]	$-(CH_2)_2C_6H_5$	2.77	-0.38	0.08	100	-	-	
					200	90	9.61 ± 0.8	
47	$-C_2H_5$	1.00	-0.07	-0.10	100	-	-	
					200	50	4.0	
					300	100	13.6	
53	$-(CH_2)_3CH_3$	2.00	-0.39	-0.13	100	-	-	
					300	100	5.10	20
55[m]	$-C_6H_5$	1.77		0.60	100	-	-	
56	$-CH_2O.C_6H_5$		0.33	0.85	100	-	-	
66	$-(CH_2)_2COCH_3$		-0.77		100	-	-	
					200	-	-	
65	$-CH=CHCH_3$	1.20		0.36	100	-	-	
					200	-	-	
68	$-CH_2C_6H_4OH$				30	-	-	100
					50	-	-	100
					100	-	-	
46	$-CH_3$	0.50	0	0	300	-	-	

Table-III: The relationship between estimated duration of action at twice the anesthetic dose and electronic (sigma*) as well as steric (Es) parameters were observed in another series of compounds.



Compound No.	R	σ^*	E_s	Estimated duration in mins. at double the anaesthetic dose
48	$-(CH_2)_2CH_3$	-0.12	-0.36	13.8
47	$-CH(CH_3)_2$	-0.19	-0.47	19.6
57	$-C(CH_3)_3$	-0.30	-1.54	30.1
54	$-CH(C_2H_5)_2$	-0.23	-1.98	32.6
52	$-CH_2C_6H_5$	0.22	-0.38	90.8
61	$-CH(C_6H_5)C_2H_5$	0.04	-1.50	96.0
62	$-CH(C_6H_5)_2$	0.41	-1.76	100.0

Table IV: 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid (alcohol) and (carboxylic acid) in order of decreasing potency.



Compound No.	R	π	E_s	σ^x	Dose mg/kg	% Anaesth.	Duration in mins.	% death
70	$-CH_2C_6H_5$	2.27	-0.38	0.22	100 300	100 100	22.40 65.10	
71	$-(CH_2)_2CH_3$	1.50	-0.36	-0.12	100 300	- 10	- 0.8	
72	$-CH(CH_3)_2$	1.30	-0.47	-0.19	300	-	-	
73	$-C(CH_3)_3$	1.98	-1.54	-0.30	100 300	- 100	- 23.50	30(100)
74	$-C_2H_5$	1.00	-0.07	-0.10	300	-	-	
75	$-(CH_2)_3CH_3$	2.00	-0.39	-0.13	100 300	- 100	- 6.8	(90)
76	$-CH_2CH(CH_3)_2$	1.80	-0.93	-0.13	100 300	- 100	- 16.3	
77	$-CH_2CH=CH_2$	1.20			100 200	- -	- -	
78	$-(CH_2)_8CH_3$	4.50			100 200	- -	- -	
79	$-(CH_2)_{10}CH_3$	5.50			50 100	- -	- -	60 (80)

4. Conclusion

In order to resolve clear understanding about Barbiturate esters as intravenous anesthetics, further extensive works are necessary on barbiturate derivatives as well as related esters of similar or diverse structural compounds could be necessary to be investigated.

Note: *This is a second part of the paper taken from my Doctoral Thesis published by Lambert Academic Publications 2017: ISBN: 978-3-330-03142-5.

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